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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,531	10/19/2001	Astrid Vrang	54320.000011	8179

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EXAMINER

VOGEL, NANCY S

ART UNIT PAPER NUMBER

1636

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/982,531	<b>Applicant(s)</b> VRANG ET AL	
	<b>Examiner</b> Nancy T. Vogel	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-11, 13-19 and 24-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 24-29 is/are allowed.
- 6) ☒ Claim(s) 1-10 and 15-19 is/are rejected.
- 7) ☒ Claim(s) 11, 13 and 14 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |  |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)            |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/4/02, 1/29/02</u> | 6) <input type="checkbox"/> Other: ____  |

## **DETAILED ACTION**

Claims 1-11, 13-19, and 24-29 are pending.

Receipt of Information disclosure statements on 10/4/02 and 1/29/02 are acknowledged.

### ***Claim Objections***

Claims 15 and 16 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 15 and 16 recited a method of producing a heterologous protein, utilizing a non-chemically defined medium, since the non-chemically defined product, i.e. yeast extract, is utilized. The claims thus fail to further limit the subject matter of the claim on which they depend, i.e. claim 1, in which chemically defined medium is utilized.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Madsen et al. (WO 98/10079) (cited by applicants).

Madsen et al. disclose a method of producing a heterologous polypeptide in a lactic acid bacterium comprising constructing a recombinant lactic acid bacterium comprising a nucleotide sequence coding for the heterologous polypeptide and operably linked thereto, appropriate regulatory nucleic sequences to control the expression of the coding sequence, cultivating said recombinant bacterium under fed-batch cultivation conditions in a chemically defined medium to express the gene, and harvesting the recombinant bacterium or the polypeptide (see claims, see pages 6 line 12 – page 8, line 15, see page ). The promoter may be regulatable, including regulation by accumulation of a metabolite intracellularly or in the medium (see page 6, lines 17-28). The lactic acid bacterium may include a signal peptide operably linked to the nucleotide sequence (see page 12 , line 19 – page 13, line 2). The reference discloses that chemically defined media may be used, and levels up to and exceeding 30 mg/L may be obtained (see page 70, lines 1-17 and page 72, lines 14-25).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. in view of deVos (Curr. Opin. 2 (3); 289-295, 1999).

Madsen et al. is cited for the reasons set forth above.

The difference between the reference and the instant claims is that a constitutive promoter is utilized.

However, de Vos disclose the use of constitutive promoters for the expression of genes in lactic acid bacteria (see page 289, second column, line 15 – page 290, second paragraph, line 9).

It would have been obvious to one of ordinary skill in the art, to have utilized a constitutive promoter as taught by deVos, in the method of producing heterologous protein disclosed by Madsen, et al., since both references disclose methods of expression of genes in lactic acid bacteria, including the use of promoters operably linked to a gene encoding a polypeptide whose expression is desired. One would have been motivated to do so by the well known properties of constitutive promoters, which include unregulated high levels of production of an operably linked gene of interest, as disclosed by de Vos.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. in view of van Asseldonk et al. (J. Bacteriol., 175, 6, 1637-1644, 1993).

Madsen et al. is cited for the reasons set forth above.

The difference between the reference and the instant claim is that a particular signal peptide, i.e. the usp45 is utilized.

However, van Asseldonk et al. disclose the usp45 signal peptide, and its use in the production of a protein in *L. lactis*. It would have been obvious to one of ordinary skill in the art, to have utilized a known *L. lactis* signal peptide such as the usp45 signal peptide, in the method of producing heterologous protein disclosed by Madsen et al., since both references disclose methods of expression of genes in lactic acid bacteria, including the use of signal peptides operably linked to a gene encoding a polypeptide whose expression is desired. ON would have been motivated to do so by the well known property of the usp45 signal peptide in directing the secretion of a heterologous protein from a lactic acid bacteria, as disclosed by van Asseldonk et al.

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. in view of Israelsen et al. (Appl. Environment. Microbiol., 61(7): 2540-2547, 1995) (cited by applicants).

Madsen et al. is cited for the reasons set forth above.

The difference between the reference and the instant claims is that the chemically defined medium is supplemented with yeast extract.

However, Israelsen et al. disclose a method of producing a heterologous protein using recombinant lactic acid bacteria (*L. lactis*), in which the culture medium is supplemented with yeast extract, i.e. that contained in M17 medium (see page 2540, right column, Materials and Methods). It would have been obvious to one of ordinary skill in the art to have added yeast extract to a culture medium for growth of lactic acid bacteria, as taught by Israelsen et al., since both Madsen et al. and Israelsen et al.

disclose culture methods for growing recombinant lactic acid bacteria such as *L. lactis*, for the production of a heterologous protein. One would have been motivated to do so by the well known advantages of using growth medium containing yeast extract, which include the ability to cultivate to high levels lactic acid bacteria such as *L. lactis*, as disclosed by the references. It is noted that M17 medium, which contains yeast extract, is the standard medium for growth of lactic acid bacteria, as taught by the reference.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 18 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of producing *S. aureus* nuclease using *L. lactis* wherein the yield is at least 200 mg/L, does not reasonably provide enablement for the production of any heterologous protein at a yield of at least 200 mg/L using any lactic acid bacterium. The specification does not enable any person skilled in the art to

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which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).



*Nature of the invention:* The nature of the invention is a method of producing a heterologous protein, using a recombinant lactic acid bacteria, wherein the yield of heterologous peptide, polypeptide or protein is at least 110mg/L or 200 mg/L.

*State of the prior art:* The prior art taught that the level of a heterologous protein produced in a recombinant microorganism is quite variable, and dependent on a multitude of factors. Madsen et al. (WO 98/10079) (cited by applicants) disclosed that in the recombinant system using lactic acid bacteria, there is a variable range of production of proteins, stating that "these differences might be caused by different chemical or physical characteristics of the individual proteins" (page 72). Therefore, the state of the prior art shows that levels of expressed protein vary depending on the protein, at least.

*Level of predictability in the art:* As set forth in Madsen et al. (WO 98/10079), one could not predict whether the levels of heterologous proteins expressed using any particular cell and vector would reach a certain level.

*Existence of working examples:* The instant specification disclosed the production of a single protein, the *S. aureus* nuclease, in a single lactic acid bacterium

*Breadth of claims:* The breadth of claims is large, encompassing any lactic acid bacterium, and any heterologous protein, using any expression system, i.e. any promoter, signal peptide, vector, etc.

*Amount of direction or guidance by the inventor.* There is little guidance provided by the specification regarding the manipulations that may be needed to obtain the levels of protein production set forth in the claims.

*Quantity of experimentation needed to make or use the invention:* Large amounts of experimentation would be needed to make the invention as claimed, since one would be required to select conditions and expression systems which would result in the very large levels of production of a heterologous protein set forth in the claims. Furthermore, there is no guarantee that any conditions would result in the levels set forth in the claims.

Therefore, the scope of the claims is not commensurate in scope with the enabling disclosure.

### ***Conclusion***

Claims 24-29 are allowed.

Claims 11, 13 and 14 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*Nancy T. Vogel*  
NANCY VOGEL, PH.D.  
PATENT EXAMINER